Hepatitis B Virus Infection in Children

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Abstract
Recent increases in Hepatitis B virus (HBV) infection prompted us to characterize HBV-infected children in Ireland and to audit management, by reviewing prospectively gathered data. Of 46 children (29 [63%] male), median age at presentation was 8.1 years (range 0.6â 17.6), monitoring duration was 22.5 months (range 1-101), 23/46 (50%) were European (including 9 [19.6%] Irish), 15 (32.6%) African and 9 (19.6%) Asian. Acquisition was vertical (25/46 [54.3%]), horizontal (5/46 [10.9%]), unknown (16/46 [34.8%]). HBV-DNA was >100,000,000 cpm in 20/32 (62.5%) with chronic infection. Hepatitis B e antigen (HBeAg) was detected in 32/44 (72.7%). We estimate that universal neonatal vaccination (UNV-HBV) could have prevented 22% of cases, and could limit further horizontal HBV spread. This supports the recent introduction of UNV-HBV.

Introduction
HBV case notification in Ireland has increased recently, from 31 notifications in 1997, to 720 in 2004 and 820 in 2006 [1]. This increase parallels increases in immigration and international adoption, and Irish emigrants returning from areas of high HBV endemnicity. WHO recommends that all children receive HBV vaccination as part of routine childhood vaccinations programmes [2]. Prior to its introduction in Ireland, we reviewed our experience of HBV infection in children in Ireland. It is common practice in general paediatric clinics in Ireland, to refer children with confirmed HBV to tertiary services, either Infectious Diseases at Our Ladyâ s Childrenâ s Hospital, Crumlin, Dublin (OLCH) and The Childrenâ s University Hospital, Temple Street, Dublin or Gastroenterology services at OLCH. The aims of this study were to characterise children diagnosed with HBV, living in Ireland and referred to either tertiary paediatric infectious diseases or gastroenterology clinics, and to audit screening for and vaccinations against co-infections in these children. We attempted to identify the mode of HBV transmission, whether patients were living in Ireland at the likely time of acquisition of infection, and to estimate the likely impact of UNV-HBV in preventing HBV infection in children who were likely to have acquired HBV infection while living in Ireland.

Methods
All HBsAg positive children and young people aged less than 19, attending Paediatric Infectious Diseases or Gastroenterology services between July 1997 and June 2006 were included. Prospectively gathered data were reviewed, supplemented by retrospective data, where necessary. Data collected included patient demographics, transmission risk, referral age, clinical and laboratory parameters, screening for co-infections and vaccination. Irish residence of an unvaccinated child at likely time of infection was deemed a vaccine-preventable case. This observational audit, as per local ethics board guidelines, did not require specific ethical approval. Acute HBV infection was defined as a clinical picture of hepatitis, with either IgM antibody to Hepatitis B core antibody (anti-HBc) or detection in serum of HBV-DNA. Chronic HBV infection was defined as persistence for more than 6 months of either HBsAg or HBV-DNA, or detectable HBsAg associated with positive anti-HBcIgG and negative anti-HBcIgM [3]. Transmission was defined as: vertical if there was evidence of either maternal HBV infection antenatally, or seroconversion peri-partum; horizontal if there was evidence of maternal HBV non-infection; unknown for all other cases.

Results
Baseline characteristics
Forty-six patients were identified: Two presented with clinical hepatitis; 44 by screening exposed infants, family contacts and children born in high endemnicity countries. Demographic data were available for all, biochemistry and serology for 45/46 (97.8%). There were 29 (63%) male and 17 (37%) female patients, median age 8.1 years (range 0.6-17.6 years). The mean duration of monitoring was 22.5 (range 1-101) months. Transmission was vertical in 25/46 (54%), horizontal in 4 (9%) and unknown in 17 (37%). The year of presentation (Figure 1) and the ethnicity of patients, defined by the country of origin of their parents, are shown (Figure 2).

Figure 1: Year of Presentation with HBV

Transmission was vertical in 11/15 children born in Ireland. Antenatal maternal HBV status was known in 5/11, 4 of whose infants received HBV-immunoglobulin and HBV vaccine following delivery. One infant received HBV vaccine at birth, 6 weeks and 6 months old but proved HBV-infected at 8 months, representing vaccine failure. Two infants presented late for the second dose (one at 6 months, one at 9 months). In both cases, delayed administration of follow-up doses may have compromised vaccine efficacy. Another infant commenced vaccination following delivery; HBsAg was weakly detected on the day of delivery and infection confirmed at 6 weeks, possibly representing in-utero transmission. The fifth child received 2 doses of vaccine prior to diagnosis of HBV. HBeAg, and HBsAg were detected at 1 month and HBV-DNA at 1 and 3 months, all of which subsequently cleared. Vaccination possibly aided recovery in this infant.

Figure 2: Country of Maternal Birth of HBV Infected Children in Ireland

Serology
Thirty-five patients had HBsAg measured at least twice, at least 6 months apart (of the remaining 11/46 patients, 6/11 had less than 6 months follow-up, 5/11 were lost to follow-up); 32/35 (91%) met the criteria for chronic HBV infection. 1/32 subsequently cleared HBsAg spontaneously. This international adoptee diagnosed at 6 months had marked asymptomatic ALT elevation, HBeAg negative, precore mutant viremia with HBV-DNA > 100,000,000cpm (copies per milliliter) at diagnosis. By 18 months there was loss of HBsAg and clearance of viremia at 2 and 3 years of age. HBeAg was detected in 32/44 (73%) patients tested.

HBV-PCR
Quantitative PCR testing for HBV-DNA was performed on 32/35 chronic HBV patients. 20/32 (62.5%) patients had >100 million cpm; 15/20 had ALT levels less than twice the upper limit of normal (ULN) (including 5/15 with normal range ALT). 3/32 (9.4%) with >100 million cpm had ALT >5 ULN; 1/3 subsequently cleared HBsAg. Twenty-six patients had simultaneous HBV-DNA quantification and HBeAg measurement. All 17 patients who were HBeAg-positive had detectable HBV-DNA. However, 8/9 HBeAg-negative patients had detectable levels of HBV-DNA; including 2/8 with HBV-DNA >100,000,000 cpm; 1/2 was proven to have a pre-core mutant. This patient was negative for HBeAg and had detectable anti-HBe antibody. (Testing for pre-core mutants was not performed routinely at this time.) One patient had undetectable HBV-DNA and undetectable HBeAg.

Follow-up
Four patients cleared HBsAg spontaneously. Two patients diagnosed with acute symptomatic HBV infection cleared HBsAg 4 and 9 months respectively after initial infection. Two infants with vertically-acquired infection cleared HBsAg, at 4 and 38 months respectively. Two patients have undergone liver biopsies, due to persistently elevated ALT and high HBV-DNA titres. The first underwent 2 biopsies; each showed minimal inflammation but without interim progression. The second also underwent 2 biopsies. The first showed fibrosis grade 3/4 and a single area of bridging fibrosis. A course of Interferon-alfa 2b was completed. Post-treatment biopsy showed persistence of fibrosis without progression. No other patient received HBV therapy.

Co-infection
Screening for co-infection was incomplete: 11/45 patients were screened for HDV; 37/45 for HCV; 28/45 for HIV; 11/45 were screened for all 3 co-infections; 17/45 for 2; 9/45 for 1; and 8/45 were not screened for any co-infection. No patient has HDV or HCV co-infection. One patient has HIV co-infection.

Vaccination
32/45 were tested for HAV susceptibility. Natural immunity was detected in 5. Only 16/27 susceptible patients have been vaccinated. Completion of family screening and appropriate HBV vaccination and precaution education was documented in 30/45 families.

Vaccine-preventable cases
Based on our criteria, 10/46 (22%) cases were potentially vaccine-preventable.

Discussion
This study demonstrates that very high viral burdens may be encountered in asymptomatic HBV-infected children, even with normal or mildly elevated ALT. This supports previous studies, that in immune-tolerant patients, transaminases may not be useful indicators of viral activity. These data also confirm that absence of detectable HBeAg does not exclude high viremia or infectivity. In this study, 31% of HBeAg negative cases had detectable viremia, of whom 2/8 had levels >100,000,000cpm. Testing for infection with pre-core mutant should be considered in children who have viremia and are HBeAg negative, especially if treatment is considered. In general, children from endemic countries with perinatally-acquired HBV infection usually remain HBeAg positive with high levels of viral replication, although histological injury is typically mild [4]. Conversely, children in non-endemic countries frequently clear HBeAg and HBV-DNA during childhood and adolescence [5]. This may be due to differences in age at infection, human or viral genetics, or route of infection. In this study, short follow-up and small patient numbers make it difficult to draw meaningful conclusions from the rate of HbeAg clearance.

In this study, co-infection rates with HIV, HCV or HDV are low, but screening was incomplete. In some cases this reflects knowledge of parental status, and corresponding absence of risk to a child; in others, screening was likely overlooked. This audit highlights the need to screen systematically for coinfection and, where screening is not indicated, to document specific reasons. HAV vaccination is recommended for HBV-infected children, yet HAV status was not determined in 28% and vaccination opportunities were missed in 41%. There are limitations to this study. Firstly, it is likely that there are children diagnosed with HBV, or who have HBV but are not diagnosed, who have not been referred to these centers. Secondly, we documented several patients in whom the mode of HBV

transmission was unclear. Transmission was classified as unknown when a reliable history was unavailable, such as for international adoptees, where either vertical or horizontal transmission could have occurred. Thirdly, follow-up (including contact vaccination and vaccination against co-infection) may have been more complete than documented (for example, where care has been transferred to other institutions). However, despite these limitations, this is the first study that attempts to characterise HBV-infected children in Ireland and will be valuable for comparison with future trends.

This study also demonstrates the problems with completion of targeted HBV-vaccination. Of 10 mother-infant pairs with vertical transmission, maternal status was known in only 5 antenatally, of whom only 4 received targeted vaccination and only 1 completed vaccination on schedule. Any Irish UNV-HBV policy will necessarily include the continuation of targeted vaccination and immunoglobulin after birth to high-risk infants. However, as these infants will receive subsequent vaccine doses with routine immunizations at 2, 4 and 6 months, it is likely that their HBV vaccines will be completed on schedule. The benefits of UNV-HBV extend beyond protection against vertically-transmitted infection, to protection against other transmission risks, including horizontal household transmission, travel to endemic areas, sexually transmitted infection, blood exposures, and intravenous drug abuse [6]. The costs of introducing and implementing universal HBV vaccination have been studied in Belgium, India, UK [7] and recently Ireland [8], and deemed cost-effective [8].

Fortunately, HBV infection prevalence remains low in children in Ireland. In 2006, 820 HBV notifications were made. These included 11 children under 15 years and 35 adolescents from 15 to 19 years [9]. In Ireland in 2006, 11% of reported HBV infections were acute, 82% chronic, and 7% unknown [9]. No acute HBV infections were reported in children under 15 years old in 2006 [9], and the incidence of newly diagnosed chronic HBV infections was less than 1/100,000 in this age group [9]. The discrepancy in numbers between our data and the statutory notifications probably reflects delayed reporting of earlier cases and delayed referral to tertiary services. Nonetheless, in this study, universal neonatal Irish vaccination could have prevented nearly one quarter of childhood cases. Other countries with similarly low HBV endemnicity also favour universal HBV vaccination [7]. Vaccination protects safely and effectively against HBV infection [10]. Previous Irish policy was to target HBV vaccination with or without HBV-immunoglobulin to at-risk infants identified by screening during pregnancy and to high-risk groups such as family contacts of HBV-infected patients. This targeted immunization failed to reduce the incidence of new infection in the U.S and was replaced by universal immunization in 1992 [11]. The change in Irish policy is to be welcomed.

Pending the development of more effective therapies for HBV infection in children, management of HBV-infected children includes regular monitoring of growth, screening for co-infection, vaccination against hepatitis A, treatment if indicated, and prevention of HBV spread. In this audit, missed opportunities included screening for co-infection, provision of HAV vaccination to HBV-infected children, and HBV screening and vaccination of household contacts. These simple but important measures should not be overlooked. Although Ireland has presently a low rate of HBV infection, universal rather than targeted HBV vaccination programmes are necessary. In this cohort, UNV-HBV could have prevented 22% of cases. UNV-HBV has now been adopted in Ireland, and is consistent with WHO recommendations.

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References

1. Murphy N, Thornton L. Epidemiology of hepatitis B in Ireland. Epi-Insight 2007; 8: 2-3.
2. Anon. Hepatitis B and breastfeeding In: WHO publications: World Health Organisation, 2006. http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/updt-22.htm. (Accessed Jan 11 2009.)
3. Anon. Case definition for notifiable diseases. Infectious disease (Amendment) (No. 3) regulations 2003 (SI NO. 707 of 2003). National Disease Surveillance Centre 2004. (Accessed Jan 11 2009).
4. Mast EE, Margolis HS, Fiore AE, et al. Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: Immunization of infants, children and adolescents. MMWR 2005; 54(RR-16):1-31. Erratum in: MMWR 2006; 55:158-9.
5. Wallace LA, Bramley JC, Ahmed S, et al. Determinants of universal adolescent hepatitis B vaccine uptake. Arch Dis Child 2004; 89: 1041-1042.
6. Bortolotti F, Cadrobbi P, Crivellaro C, et al. Long term outcome of chronic type B hepatitis in patients who acquire hepatitis B infection in childhood. Gastroenterology 1990; 99: 805-10.
7. English P. Should universal hepatitis B immunisation be introduced in the UK? Arch Dis Child 2006; 91: 283-6.
8. Tilson L, Thornton L, O'Flanagan D, Johnson H, Barry M. Cost effectiveness of hepatitis B vaccination strategies in Ireland: an economic evaluation. Eur J Public Health Jan 3 2008; The European Journal of Public Health, doi:10.1093/eurpub/ckm123 [Epub ahead of print] (accessed on Jan 11 2009).
9. Anon. Infectious Disease Notifications in Ireland, 2004-2006. Health Protection Surveillance Centre. In: Health Services Executive, Dublin, 2007. http://www.ndsc.ie/hpsc/NotifiableDiseases/AnnualIDStatistics/File,2393,en.pdf (accessed on Jan 11 2009)
10. Lyon B. World Health Organisation, Department of Communicable Diseases Surveillance and Response. Hepatitis B. World Health Organisation 2002; 1-76.
11. Anon. Editorial Note. MMWR 1999; 48:780-782. http://www.cdc.gov/MMWR/preview/mmwrhtml/mm4835a3.htm (Accessed on Jan 11 2009)

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